REMARKS

After entry of this amendment, claims 19-24, 26-34, 37-39, and 41-43 are pending, of which claims 22-24, 29-34, 37-39, and 41-43 are withdrawn. Claims 25, 35-36, 40, and 44 have cancelled without prejudice or disclaimer. The subject matter of the cancelled claims 25, 40, and 44 have been incorporated into the amended claims 19, 26, and 28, respectively. The claims have been amended without prejudice or disclaimer to delete the non-elected subject matter, to better comply with the U.S. practice, and to address various points made in the Office Action. The amended claims find support *inter alia* in the original claims. Further support for the amendment made in claims 19, 26, and 28 is found in the specification at page 18, lines 17-18. No new matter has been added.

Claim Objection

Claims 19-21, 25-28, 35-36, 40, and 44 were objected to for containing non-elected subject matter. The objection is believed to be rendered moot in view of the amendment and is respectfully requested to be withdrawn.

Rejections under 35 U.S.C. § 112

Claims 19-21, 25-28, 35-36, 40, and 44 were rejected under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the written description requirement and for lack of an enabling disclosure. Applicants respectfully disagree and traverse the rejections.

Enablement Rejection

The Examiner rejects the claims for lack of enablement, alleging that the specification is only enabled for the promoter sequences of SEQ ID NOs: 11-14. Applicants respectfully disagree. However, to expedite prosecution, the claims have been amended without prejudice or disclaimer to recite the promoter used in the claimed method with more specificity. Applicants respectfully request reconsideration in light of the amendment and for the following reasons.

The Examiner alleges that the specification does not provide guidance for any CHRC promoter from any species other than SEQ ID NOs: 11-14. The Examiner argues that the function of promoter fragments and sequence variants in transgenic plants and deletion analysis of promoters is unpredictable, citing Kim *et al.* (hereinafter "Kim") and Donald *et al.* (hereinafter "Donald"), respectively. The Examiner further alleges that the function of promoter

fragments and sequence variants in transgenic plants is unpredictable when the promoter function is regulated by conditional elements, citing Dolferus *et al.* (hereinafter "Dolferus"). The Examiner concludes that undue experimentation would be required to develop and evaluate all promoter-effective molecules that would give floral specific expression in Tagetes as claimed. It is respectfully submitted that Kim, Donald, and Dolferus do not support the position alleged by the Examiner. Rather, these references support enablement, *inter alia*, by showing that the essential promoter elements occupy only a small fraction of a promoter sequence, which in turn implies that the vast majority of a promoter sequence may be modified or deleted **without** affecting promoter activity.

Specifically, the Examiner argues that Kim shows that mutation of a single nucleotide significantly altered the strength of expression, while deletions in other regions of the promoter completely eliminated function. However, Kim actually supports enablement. The mutation described in Kim was not a random mutation of a promoter sequence, but a mutational analysis of an essential part of 30 nucleotides of the *nos* promoter (pages 106 and 107, first paragraphs right column). This short nucleotide sequence selected by Kim contains two hexamer motifs surrounding a spacer region of 8 nucleotides (page 108, Table 1). By replacing this essential part with mutated oligomers (page 107, full right column), Kim demonstrated the importance of the two hexamer sequence elements. Kim thus found that promoters consist of essential elements which can readily be identified with the help of deletion experiments in combination with a standard search for sequence motifs. The symmetric structure of the hexamers identified by Kim is readily visualized by a person skilled in the art. A symmetric structure consisting of a spacer region surrounded by hexamers or palindromes can be identified by pure sequence analysis with or without the help of computer algorithms. Furthermore, Kim supports a proposition that mutations in these sequence elements do not necessarily abolish promoter activity. To the contrary, Kim shows that only 20 nucleotides out of 30 identified by deletion analysis are important for promoter activity. Kim also shows that mutations in the 20 nucleotides left, like changing one hexamer of the sequence to a palindrome, does improve promoter activity. Changing the spacer region to a symmetric sequence does improve the promoter activity even further (page 110, Table 3, *nos*, 128-CG and *ocs*). Thus Kim discloses that a 30 base pair element can be narrowed down to 20 nucleotides, of which 10 can be mutated, loosing promoter activity only in two constructs. Thus Kim has demonstrated that even in this small element of 30

base pairs, shown to be essential for promoter activity, more than 30% of the bases can be mutated without loosing the activity.

The Examiner cites Donald to support the allegation that promoter deletion analysis is unpredictable. Rather Donald defined a 196-bp long fragment of the *Arabidopsis thaliana* rbc8-1A promoter as being essential and sufficient for promoter activity (page 1717, Abstract). Donald also showed that this promoter fragment had the capacity to direct expression independent of its orientation and relative position in the *Adh* promoter. Further sequence analysis showed that this promoter fragment contained further promoter elements necessary for its activity (page 1717, Abstract and page 1720, Figure 3). Donald also disclosed that the expression pattern of the promoter fragment can be influenced by other active promoter fragments and enhancing elements contained in the CaMV promoter fragment and the *Adh* promoter used by Donald (page 1724, last paragraph). This does not show that promoter deletion analysis is unpredictable. Rather Donald showed that active fragments and elements from other promoters could restore activity following mutations in essential boxes (see Abstract and page 1724). Donald also demonstrated that a promoter fragment identified by deletion analysis can be used independent of its orientation and relative position and still preserve its activity, as long as particular sequence elements like the G-, I- or GT-box are not destroyed by mutation (page 1724, last paragraph). Those boxes have a size of only 12 to 14 base pairs (page 1720, Figure 3) and represent only a minor part of the rbcS-1A LRE sequence of 196 base pairs. Moreover, as in Kim, the mutations described in Donald were site-specific mutations in conserved sequences and not random mutations (see Abstract).

Dolferus discloses a detailed analysis of an inducible promoter of about 1 kb in length from *Arabidopsis*. By using only 5 deletion constructs, Dolferus showed that the promoter contained four different regions (regions I, II, III and IV), of which region I was responsible for preventing noninduced expression. Region II contained a positive regulatory element necessary for high level expression. Regions III and IV were the most critical regions for promoter activity. These two regions contained five small promoter elements (page 1075, Abstract). Further mutational analysis of these small promoter elements, having a size between 7 and 28 base pairs, showed that only four of them were necessary for preserving promoter activity (page 1085, Figure 6). Dolferus by a simple sequence analysis identified critical regions of the

promoter which when mutated affected promoter activity. Analogous to the disclosure of Kim and Donald, the mutations done by Dolferus were not random. This strategy is clearly stated by Dolferus "Site-specific mutagenesis (Kunkel *et al.*, 1987) was used to introduce mutations at four specific regions of the CADH fragment ...." (page 1076, first quarter of right column). Dolferus did not show any data of mutations in regions outside the identified sequence elements, but that mutations in essential regions affected promoter activity. Thus, Dolferus demonstrated through simple deletion experiments, in combination with a search for known or predicted promoter boxes, that a person of skill in the art could identify which regions or elements of the promoter are essential for preserving function and any mutations in the essential elements would affect activity.

All three references cited by the Examiner show that promoter fragments with a particular activity can be identified by standard deletion experiments, that essential sequence elements can be predicted and identified by sequence analysis, and that those sequence elements represent only a minor part of the promoter sequence. By showing which parts of the promoter sequence are essential through routine experimentation and that only small parts of the original promoter sequence are necessary for activity, Kim, Donald, and Dolferus demonstrate that it is readily within the skill of the art to determine which parts of a promoter sequence can be changed, which substitutions can and cannot be made which will affect activity. A skilled artisan would recognize most of a promoter sequence might be changed without losing promoter activity.

Furthermore, identifying regions of a particular promoter sequence that are essential for the specific promoter activity is routine and not undue. As known to one skilled in the art, regions essential for promoter activity often demonstrate clusters of certain, known promoter elements. Such promoter elements can be identified by art-recognized computer algorithms that are specifically developed and adopted for the analysis of plant genes. Once identified, it would be apparent to one skilled in the art which regions of the promoter sequence are likely important to the promoter function and should not be modified in light of the teaching in Kim. Conversely, regions identified as low or no importance for promoter function would be expected to be more tolerant to modification or deletion as shown in Donald and Dolferus. Numerous computer algorithms and databases were made publicly available for such prediction at the time of filing,

such as PLACE (Higo et al., Nucleic Acids Research, 1999, 27(1): 297-300), the BIOBASE database "TRANSFAC" (Wingender et al., Nucleic Acids Research, 2001, 29(1): 281-283 and Matys et al., Nucleic Acids Research, 2003, 31(1): 374-378) and the database PlantCARE (Lescot et al., Nucleic Acids Research, 2002, 30(1): 325-327), just to name a few. The applicability of these algorithms and databases in promoter elements prediction can be further evidenced by Steffens et al. (Nucleic Acids Research, 2004, 32: D368-D372), where an Arabidopsis genomic map for transcription regulatory factor binding sites (*i.e.* AthaMap) was created with the aid of the database TRANSFAC and the pattern search program Patser. The creation of AthaMap demonstrates that one skilled in the art would be able to predict the transcription factor binding sites within a sequence of interest using the publicly available databases and pattern search programs and algorithms before carrying out actual experimentation to refine and/or validate the computer predicted sequence information or to modify or delete the promoter sequence while maintaining the promoter activity.

Even further, as discussed in Kolchanov *et al.* (Nucleic Acids Research, 2002, 30(1): 312-317) and Sandelin *et al.* (Nucleic Acids Research, 2004, 32: D91-D94), the importance of single nucleotides of a transcription factor binding site can be predicted and determined using these computer programs. Together with the teaching of Kim, one skilled in the art would know to avoid introducing any modification, change, or deletion into those nucleotides in order to preserve the promoter activity. In sum, these references evidence the availability of the various different databases and sequence analysis tools that are specifically designed and adopted to predict the promoter elements at the time of filing. Additionally, these references further demonstrate that a skilled artisan would be able to identify important parts of a promoter sequence using these databases or sequence analysis tools. Once a transcription factor binding site profile of a particular sequence is obtained, one skilled in the art would be able to identify regions of promoter sequence that can be modified or deleted without affecting the promoter function using any conventional method known in the art.

Additionally, the present application provides detailed guidance on isolating and cloning the CHRC promoters into a vector as exemplified in Example 6C at page 66, on producing transgenic Tagetes plants in Example 7 at page 68, and on determining the gene expression as exemplified in Examples 8 and 9 at pages 70 and 72, respectively. In view of the detailed

description and guidance provided in the specification as exemplified above, one skilled in the art would recognize that screening and testing for promoter activity is routine and is not undue experimentation. The same applies to screening and testing the promoter activity of fragments of SEQ ID NO: 11 as claimed in the present application, as evidenced by Kim, Donald, and Dolferus cited by the Examiner. It is therefore respectfully submitted that determining the functional activity of individual species of the limited genus being claimed is routine experimentation and not undue experimentation. Compare, *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988) (routine screening of hybridomas was not "undue experimentation;" the involved experimentation can be considerable, so long as "routine"). The test for whether experimentation is "undue" is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed. *Ex parte Jackson*, 217 USPQ 804, 807 (1982). In the present case, the specification provides detailed guidance and teaches in the Examples, as explained above, the types of routine assay which are employed to confirm the promoter activity in directing the gene expression. The detailed guidance provided in the present specification and the routine nature of the screening for the promoters useful in practicing the claimed method overcome the unpredictability alleged by the Examiner.

Thus, from a promoter sequence and a description of its promoter activity, a person of ordinary skill in the art can readily identify related promoter fragments with promoter activity and the important sequence elements contained therein by using routine experimentation as described in the present application and as demonstrated by Kim, Donald, Dolferus, and other additional references discussed in this response. Furthermore, the person of skill in the art can readily identify the nucleotides in the promoter sequence which are not essential to the promoter activity and might be changed or deleted without affecting the promoter activity. By using routine experimentation, a person skilled in the art would be readily able to construct promoter fragments that preserve the desired promoter activity.

In view of the detailed description, guidance, working examples, and high level of skill, the specification enables the full scope of the present claims without undue experimentation. On

these facts, an analysis under *In re Wands* supports enablement. For these reasons and in light of the amendment, reconsideration and withdrawal of this rejection is respectfully urged.

Written Description Rejection

The Examiner alleges that the specification only describes the full length of SEQ ID NOs: 11-14 for use as promoter sequences but not any other promoter sequences as claimed. The Examiner further alleges that the specification fails to provide structural features of the promoter sequences which correlate to the petal-specific expression. Applicants respectfully disagree. However, in order to expedite prosecution, the claims have been amended without prejudice or disclaimer to recite the promoter sequences with more specificity. Applicants respectfully request reconsideration in light of the amendment and for the following reasons.

The guidelines for applying the written description requirement is stated in the "Guidelines for Examination of Patent Applications Under the 35 U.S.C. § 112, 1, Written Description Requirements" 66 Fed. Reg. 1099, 1106 (Jan. 5, 2001). As there indicated, the written description requirement as applied to a claim reciting a genus can be satisfied in a number of **alternative** ways, such as through sufficient description of a representative number of species by actual reduction to practice, by disclosure of relevant identifying characteristics, by functional characteristics coupled with known or disclosed correlation between function and structure, or by a combination of such identifying characteristics.

As stated in *Eli Lilly and Co.*, "[a] description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs." 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). Because each and every embodiment within a claim need not be disclosed, it is respectfully submitted that the specification provides a representative number of species under the standard of *Eli Lilly and Co.* in light of the present amendment. *See also In re Angstadt*, 537 F.2d 498 (CCPA 1976) (holding that there has never been a requirement that every species encompassed by a claim must be disclosed or exemplified in a working example). Accordingly, the claims as claimed satisfy the written description requirement.

For at least the above reason, it is respectfully submitted that the amended claims have overcome the written description rejection. Reconsideration and withdrawal of the rejection is respectfully requested.

Rejections under 35 U.S.C. § 103

Claims 19-21, 25-28, 35-36, 40, and 44 were further rejected under 35 USC § 103(a) as being obvious over Hauptmann *et al.* (US Patent 7,223,909, hereinafter "Hauptmann") in view of Vishnevetsky *et al.* (Plant J., 1999, 20: 423-431, hereinafter "Vishnevetsky").

The Examiner relies on Hauptmann for teaching a transgenic *Tagetes erecta* transformed with a transgene that contains a promoter directing a flower-preferred gene expression, and a method of expressing one or more genes. The Examiner acknowledges that Hauptmann does not teach the CHRC promoter, but relies on Vishnevetsky for such teaching. According to the Examiner, one skilled in the art would be motivated to modify the method and plant taught in Hauptmann by using the promoter of Vishnevetsky because Hauptmann suggests the use of flower-specific promoters. The Examiner further relies on the direct link of the CHRC promoter to carotenoid accumulation for the finding of obviousness, motivation to combine, and reasonable expectation of success. Applicants respectfully disagree and urge reconsideration of the rejection for the following reasons.

As stated in MPEP 2143.02(III), whether an art is predictable or whether the proposed modification or combination of the prior art has a reasonable expectation of success is determined at the time the invention was made. As discussed in the specification at page 3, lines 25-28, numerous flower-specific promoters from various organisms are known in the art at the time of filing. However, many of these art-known promoters do not direct expression of genes in a flower-specific or petal-specific fashion in plants of the genus Tagetes. Therefore, it is respectfully submitted that there would have been no reasonable expectation of success, as alleged by the Examiner, that a combination of the method taught in Hauptmann with the promoter of Vishnevetsky would provide the desirable result as shown by the inventors of the present application.

Reconsideration and withdrawal of the obviousness rejection is respectfully requested.

CONCLUSION

For at least the above reasons, Applicants respectfully request withdrawal of the rejections and allowance of the claims.

Applicants reserve all rights to pursue the non-elected claims and subject matter in one or more divisional applications.

Accompanying this response is a petition for a three-month extension of time to and including March 18, 2008 to respond to the Office Action mailed September 18, 2007 with the required fee authorization. No further fees are believed due. If any additional fee is due, the Director is hereby authorized to charge our Deposit Account No. 03-2775, under Order No. 13173-00026-US from which the undersigned is authorized to draw.

Respectfully submitted,

By

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